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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,664	08/15/2002	Mou Tuan Huang	RU-0103-US	2837

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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,664	HUANG ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) 1-11 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10/11/02 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants to note that the correct Serial Number of your Application under prosecution in the USPTO is 10/088,664. Please ensure that the correct U.S. Serial Number for this application is cited in all future correspondence with this Office.

2. The assigned Examiner to your application in the USPTO is Dr. Kailash C. Srivastava. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner K.C. Srivastava in Art Unit 1651.

3. Claims 1-11 are pending and are examined on merits.

Information Disclosure Statement

4. The information disclosure statement filed 11 October 2002 is entered and considered.

Priority

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. §112 for claims 1-2, 4 and 7-11 of instant application. Claim 5 is dependent on Claim 1 and Claim 6 is dependent on Claim 5. Consequently, priority benefit for filing date of September 21, 1999 is given to the claim (i.e., Claims 3) drawn to a method to inhibit tumor cell growth. Since all other claims (i.e., 4, -11) are either directly or indirectly dependent on either Claim 1 or Claim 2, Claims 1-2 and 4-11 are assigned the priority date of 08/15/2002 which is the filing date for instant non-provisional U. S. Application Number 10/088,664.

Claim Rejections - 35 U.S.C. § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

7. Claims 3-11 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while enabling for a method to treat cancer via administering a composition comprising reseveratrol (See Page 12, Line 4 to Page 14, Line 19), does not reasonably provide enablement for a method to prevent cancer via instantly claimed method of administering the instantly claimed pharmaceutical composition comprising orange peel extract/ components of orange peel extract either alone or in mixture with

extracts of other plants as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

From the record of the present written disclosure applicants have merely demonstrated under in-vivo and in-vitro experimental conditions, lesser incidence of cancer in animals that were administered a composition comprising a certain quantity of resveratrol (see specification Page 12, Line 4 to Page 13, Line 16).

8. Claims 5, 7 and 10 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while enabling for a method to reduce the incidence of cancer in the experimental group that was administered a composition comprising resveratrol in contrast to the control group (See Page 12, Line 4 to Page 14, Line 19), does not reasonably provide enablement for a method to prevent cancer via instantly claimed method of administering the instantly claimed pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

From the record of the present written disclosure applicants have merely demonstrated under in-vivo and in-vitro experimental conditions, lesser incidence of cancer in animals that were administered a composition comprising a certain quantity of resveratrol.

Inventions targeted for human therapy claiming method(s) of prevention of a certain ailment bear a heavy responsibility to provide supporting evidence because of the unpredictability of the biological responses to therapeutic treatments. THE STANDARD OF ENABLEMENT IS HIGHER FOR SUCH INVENTIONS because effective treatment or prophylaxis of disease conditions are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to human that would in effect "prevent" the condition/ailment from happening require supporting evidence because of the unpredictability in biological responses to therapeutic treatments or therapeutic prophylaxis. In order to enable the skilled artisan to practice the invention as claimed, applicants would have to demonstrate the functional effect and describe the therapeutic effect or prophylactic effect, and describe the effective amounts of each ingredient of the composition for the administration of the composition intended for a method of therapeutic treatment or prophylaxis. THERE IS NO GUIDANCE IN THE SPECIFICATION, other than a method to administer a composition comprising reservation for the treatment and/or prevention of aforementioned disease condition. MOREOVER, THE INSTANT APPLICATION DOES NOT PROVIDE A WORKING EXAMPLE PROVIDING DATA THAT SHOWS THAT THE METHOD AND COMPOSIOTION OF THE INSTANTLY CLAIMED INVENTION (i.e., a composition comprising orange peel extract/ components of

orange peel extract either alone or in mixture with claimed extracts from other plants WOULD INDEED PREVENT AN EVENT SUCH AS THE CLAIM DESIGNATED DISEASE CONDDITIONS. THUS, APPLICANTS HAVE NOT DEMONSTRATED THE CLAIMED FUNCTIONAL EFFECT OF TREATING AND/OR PREVENTING ANY AND ALL LOW-RENIN HYPERTENSION, SALT-SENSITIVE HYPERTENSION OR LOW-RENIN, SALT SENSITIVE HYPERTENSION.

Accordingly, undue experimentation without a reasonable expectation of success as to how to determine which combination of orange peel extract or components of orange peel extract with a pharmaceutically acceptable carrier in which therapeutic amounts of any or all of the claimed designated components would be effective in the instantly claimed method to administer the instantly claimed composition to obtain the instantly claimed functional effect of treating and/or preventing cancer and which type of cancer would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

9. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

10. Claims 2-11 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claims 2,4 and 6-11 are rendered vague and indefinite by the term "extract" because this term, in and of itself, does not adequately delineate its metes and bounds. This term is best defined as a product-by process since product-by-process claims are intended to define products that are otherwise difficult to define (and/or distinguish from the prior art). For example, is the extract obtained by extraction with water, a polar solvent, a non-polar solvent, an acid or base, a squeezed extract, or something else? In addition, from what part(s) of the plant is the extract obtained? It is well accepted in the herbal art that extraction with one of various distinct solvents, as well as from particular parts of therapeutic plants, has a profound impact on the final product with respect to the presence, absence, amounts, and/or ratios of active ingredients therein and, thud, its ability to provide the necessary functional effect(s) instantly claimed and/or disclosed. Since the extract itself is clearly essential to the claimed invention, the steps(s) by which the claimed extract is obtained are also clearly essential and, therefore, must be recited in the claim language itself

(i.e., as a product-by-process). Please note that although claims are interpreted in light of the specification, critical limitations from the specification can not be read into the claims (see, e.g., *In re* Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (DED. Cir. 1991). Accordingly, without the recitation of all these critical limitations as set forth above, the claims do not adequately define the instant invention.

Claim Rejections – 35 U.S.C. § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

12. Claim 1 is rejected under 35 U.S.C. §102(b) as anticipated by Nagy et al. (Citrus Science and Technology, 1977, AVI, Westport, Volume 1, Pages 416-417)

Claim recites a composition comprising an orange peel extract containing at least three polymethoxylated flavones and a physiologically acceptable carrier or excipient.

Nagy et al. disclose citrus compositions comprising 4', 5,6,7,8, pentamethoxyflavone (i.e., tangeritin) 5,6,7,3', 4'-pentamethoxyflavone (i.e., sinensetin) and 5,7,8,3', 4'-methoxyflavone (Page 415, Lines 32 to Page 417, Line 6). Since these compounds are present in citrus fruit or different Citrus varieties, Nagy et al. inherently teach a composition comprising at least three polymethoxylated flavones in a physiologically acceptable carrier or excipient (i.e., citrus juice or water).

Therefore, the reference deems to anticipate the cited claim.

13. Claims 1,3,5, 7-8 and 10-11 are rejected under 35 U.S.C. §102(b) as anticipated by Attaway (Citrus Science and Properties". Food Phytochemicals for Cancer Prevention. ACS Symposia Series, //546. Pp. 240-248) with evidence from Malterud et al. (J. Agric. Food Chem., 2000, 48, Pages 5576-5580).

Attaway teaches that polymethoxyflavanoids, e.g., tangeritin and nobiletin are more potent tumor cell growth inhibitors and possess anticarcinogenic activities (Abstract, Lines 1-9). Attaway further teaches that citrus juice flavonoids possess anticarcinogenic and antitumor agents (Page 240, Lines 19-20). Since citrus juice are taught to have these flavonoids possessing said activity, inherently, Attaway teaches a composition comprising polymethoxyflavanoids in a physiologically acceptable carrier or excipient because juice constitutes water and water is a physiological excipient. Attaway also points to the teaching about anticarcinogenic activity of edible foods (Page 242, Lines 3-6 after Figure 1) and

antiproliferative effects of citrus flavonoids to human squamous cell carcinoma "in-vitro" (Page 243, Lines 34-36). Thus, teachings from Attaway clearly show antitumor and anticarcinogenic activities of citrus flavones that are: tangeritin, nobelitin and sinensetin (See Malterud et al., Abstract, Lines 1-4) when administered to humans as an edible food. Thus, Attaway teaches a method to inhibit tumor cell growth and a method to treat cancer (i.e., squamous cell carcinoma) with a nutraceutical composition comprising citrus flavones (i.e., citrus juice, see Attaway, Page 242, Lines 1-8 under the subheading "Anticarcinogenic Activity of Citrus Favonoids").

Therefore, the reference is deemed to anticipate the cited claims.

In this rejection under 35 U.S.C. §102(b), Malterud et al. (J. Agric. Food Chem., 2000, 48, Pages 5576-5580) is cited to merely support disclosure of at least three flavone constituents of citrus juice and not as a prior art reference.

Claim Rejections - 35 U.S.C. § 103

14. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C.§ 103(a).

16. Claims 1-11 are rejected under 35 U.S.C. § 103 (a) as obvious over Nagy et al. (Citrus Science and Technology, 1977, AVI, Westport, Volume 1, Pages 416-417) and Attaway (Citrus Science and Properties". Food Phytochemicals for Cancer Prevention. ACS Symposia Series, //546. pp. 240-248) with evidence from Malterud et al. (J. Agric. Food Chem., 2000, 48, Pages 5576-5580) in view of Peirce (The American Pharmaceutical Association Practical Guide to Natural Medicines, 1999, Stonesong Press, Inc., Pgs .563-566), Madis Botanicals (Madis Botanicals, Inc., Resverapure™ Resveratrol PE 8%, Product Code 04544, Page 2, Lines 6-7 and 15-31, 1997), Castleman (The Healing Herbs, The Ultimate Guide to the Curative Power of Nature's Medicines, 1991, Rodale Press, Emmaus, PA. Page 349, Column 2, Lines 3-10), Thomas (U. S. Patent 5,830,738) and Bailey et al (U.S. Patent 5,859,293).

Claims recite a nutraceutical composition comprising a physiological carrier/excipient, a minimum of three hydroxy flavone obtained from orange peel extract, and at least one other compound among: rosemary extract, Mexican bamboo extract, Huzhang extract, resveratrol, black tea extract, and a hydroxylated or methoxylated resveratrol analog. Claims also recite a method to inhibit tumor cell growth/ treat cancer by administering said composition to an individual in need thereof.

Teachings from Nagy et al. and Attaway have already been discussed *supra.* Nagy et al. and Attaway's teachings however, do not disclose the nutraceutical or dietary supplements containing said flavones, with other plant extracts (claimed in Claims 2 and 6) for inhibiting tumor development or prevention of cancer.

Thomas et al. beneficially teach that carotenoid pigments obtained from orange peels and other plants prevent cancer upon ingestion of these chemicals (Column 1, Lines 22-62). Peirce discloses that rosemary extract helps fight cancer and has been shown to significantly inhibit development of breast cancer (Page 553, Lines 5-7). Bailey et al., (Column1, Lines 29-34 and Column 2, Lines 10-15) and Peirce (Page 553, Lines 5-7) teach inhibition or delayed onset of certain types of cancers when extracts from rosemary and other plants are ingested. Madis Botanicals (Page 2, Column 1, Lines 6-7 and 15-31) teaches powdered nutraceutical and dietary supplement preparations of resveratrol obtained from Huzhang or knotweed to inhibit carcinogenesis or tumerogenesis. Madis Botanicals also discloses that Huzhang or knotweed or Mexican bamboo or giant knotwood are all *Polyganum cuspidatum* and resveratrol is an antioxidant obtained from this plant species. Castleman teaches that black tea has antioxidants and therefore, it may also be helpful in cancer prevention. All the references cited also disclose that the plant extracts cited herein are comprised of antioxidants and it is the antioxidant component of these plants that is effective in either inhibiting or late onset of different types of cancer.

A person of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings from different prior art references cited *supra* to obtain a pharmacetical/nutraceutical composition comprising extract from orange peel containing at least three flavones and to administer said pharmaceutical/ nutraceutical composition to an individual in need thereof to treat cancer or inhibit tumor growth; because all of the prior art references (Attaway, Thomas et al., Bailey et al., Peirce and Madis Botanicals) teach inhibition or delayed onset of certain types of cancers when compositions comprising extracts from orange peel, rosemary, Huzhang, Mexican bamboo and composition containing resveratrol (a compound obtained from Huzhang) are ingested by a mammal in need thereof. Attaway with evidence from Malterud et al. remedies the deficiency in teachings of Nagy et al., that compositions comprising orange peel extract flavones and a pharmaceutical carrier reduce tumor growth, while Thomas remedies the deficiency that orange peel extract is anticarcinogenic. Pierce

and Bailley et al. remedy the deficiency of rosemary extract having anticarcinogennic property, Castelman remedies the deficiency of the anticarcinogenic property in tea and Madis Botanicals remedies the deficiency of reservatrol or Huzzhang, or Mexican bamboo in the teachings from Nagy et al.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine teachings from all of the prior art references to obtain a nutraceutical/ pharmaceutical composition and to administer said composition to an individual in need thereof to inhibit some types of cancer or tumor growth. Also known in the art are the nutraceutical and dietary supplements of these plant extracts and that ingestion of that composition inhibits tumor growth/cancer. None of the prior art references cited above teach administering said composition in a certain form (e.g., tablet, liquid, or capsule) via inhalation, injection, rectally or vaginally. However, the adjustment of particular conventional working conditions (e.g., mode or form of administration of a composition) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter that is well within the purview of the skilled artisan.

From the teachings of the cited references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

17. No Claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (703) 605-1196. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743 Monday through Thursday. The fax phone number for the organization where this application or proceeding is assigned is (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1651
(703) 605-1196

November 13, 2003

CHRISTOPHER R. TATE
PRIMARY EXAMINER